Microfluidic System for More Physiologically-Relevant In Vitro Measurement of Cell Function

NIST is developing new microfluidic systems to better measure phenotypic and molecular characteristics of cells and groups of cells. The project is addressing technical hurdles of integrated microfluidic cell-based measurement systems by; 1) engineering reproducible microfluidic systems that will provide control and evaluation of the cellular microenvironment, and 2) integrating in a single microfluidic system multiple quantitative cell-based analysis capabilities. The new NIST measurement technology is expected to enable new innovations in several fields, most notably, drug development and discovery.

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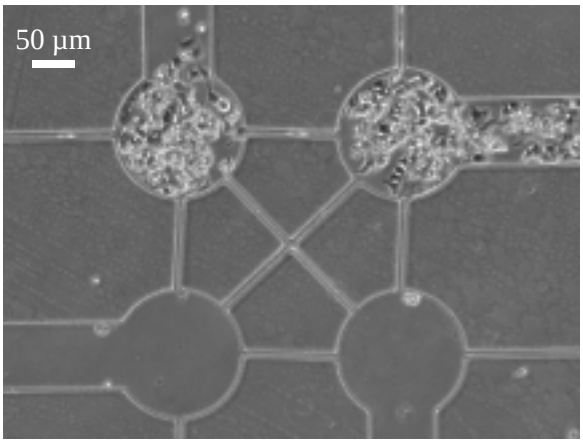
Cell-based assays are utilized extensively in the biotechnology and pharmaceutical industries during multiple phases of product and drug development. Despite their widespread use, their predictive capabilities are lacking, owing in part to the poor environmental control provided by conventional cell culture strategies, and few strategies for generating quantitative, correlated measurement data. Establishing robust and predictive metrics for cellular outcomes and behaviors in artificial cell culture environments has become an enormous hurdle to studying biological systems. Existing measurement tools for evaluating cellular systems are severely limited: in addition to offering poor environmental control, analyses in these systems typically produce qualitative and descriptive data, and different measurement modalities are not correlated. The appetite for quantitative and correlated measurements under well-controlled conditions is enormous, but measurement tools are lacking.

NIST is engineering reproducible microfluidic cell-based assay systems for simultaneous multi-mode analyses for better understanding of complex biological systems.

Cell behavior is powerfully modulated by local extracellular cues. However, the number of parameters that effect cell behavior is large, and include soluble signaling molecules, dissolved gases, the chemistry and mechanics of the insoluble extracellular matrix proteins, and the actions of neighboring cells. Additionally, cells respond to spatial and temporal variation in these environmental cues.

Micro- and nano-fabricated microfluidic systems can provide a level of control over the cell culture microenvironment that cannot be achieved in traditional culture condition such as plastic plates. Microfluidics systems can reproducibly produce confined and well-defined systems on the cellular length scale (~5µm - 500µm) and can incorporate complex designed topographies, densities of extracellular matrix signaling molecules, nonrandom organization of cells of different type, and ability to mimic *in vivo* solution flow. Microfluidic cultures can be designed to be small and massively parallel for application in high throughput drug or toxin screening on small, defined cell populations.

Flow within the microfluidic system will be used to precisely stimulate and interrogate cells with high spatial and temporal resolution. Control of the cellular environment vis a vis extracellular matrix proteins, hormones, cytokines and other cell stimuli can in principle be achieved on a scale of a few microns. Recent technological advances in polymer microfluidic systems provide a definable, precise platform for configuring engineered biomimetic microenvironments.



Prototype microfluidic device enables controlled introduction of cells and delivery of soluble bioactive molecules.

Additionally, microfluidic systems will enable integration of cell culture with automated analysis on the same device. The microfluidics device will provide access to optical imaging, electrochemical interrogation, and controlled lysis of desired cells and collection of cell contents for downstream analysis is envisioned. There has been significant development in the field of analytical capabilities within microfluidic devices. These enable integration in a single device of sensitive cell-based assays with a well-controlled microenvironment for continuous monitoring of the cell culture. Alternately, the microfluidic systems can provide sample prep for off-device analysis via amplification or preconcentration.